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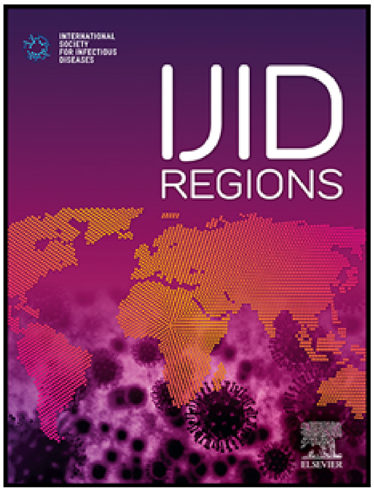

Prognostic value of biochemical parameters among severe COVID-19 patients admitted to an intensive care unit of a tertiary hospital in South Africa

Annalise E. Zemlin , Brian Allwood , Rajiv T. Erasmus , Tandi E. Masha , Zivanai C. Chapanduka , Thumeka P. Jalavu , Vera Ngah , Lovemore N. Sigwadhi , Coenraad F. Koegelenberg , Elvis Irusen , Usha Lalla , Anteneh Yalew , Nicola Baines , Jacques L. Tamuzi , Anne K. Barasa , Valerie Kemunto Magutu , Caroline Njeru , Angela Amayo , Marianne Wanjiru Mureithi , Mary Mungania , Musa Sono-Setati , Alimuddin Zumla , Peter S. Nyasulu , for the COVID-19 Rapid Research Response Collaboration

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Highlights

- COVID-19 associated with biochemical prognostic markers in the ICU
- Biochemical risk predictors of COVID-19 severity and corresponding poor outcome
- LDH and NTProBNP as independent risk factors of a poor prognosis in the ICU
- More investigations on predictors of COVID-19 severity and morality in the ICU

Prognostic value of biochemical parameters among severe COVID-19 patients admitted to an intensive care unit of a tertiary hospital in South Africa.

Short Title: Biochemical parameters in severe COVID-19

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Abstract

Background：Data on biochemical markers and their association with mortality rates observed in patients with severe COVID-19 disease admitted to Intensive Care Units (ICUs) in sub-Saharan Africa are scanty. We performed an evaluation of baseline routine biochemical parameters as prognostic biomarkers in COVID-19 patients admitted to ICU.

Methods：Demographic, clinical, and laboratory data were collected prospectively on patients with PCR-confirmed COVID-19 admitted to the adult ICU in a tertiary hospital in Cape Town, South Africa, between October 2020 and February 2021. Robust Poisson regression methods and receiver operating characteristic (ROC) curve were used to explore the association of biochemical parameters with severity and mortality.

Results：A total of 82 patients [(median age 53.8 years (IQR: 46.4-59.7)] were enrolled, of whom 27 (33%) were male. The median duration of ICU stay was 10 days (IQR: 5-14); 54/82 (66% CFR) patients died. Baseline lactate dehydrogenase (LDH) (aRR: 1.002, 95%CI: 1.0004-1.004; P = 0.016) and N-terminal pro B-type natriuretic peptide (NTProBNP) (aRR: 1.0004, 95%CI: 1.0001-1.0007; P = 0.014) were both independent risk factors of a poor prognosis with optimal cut-off values of 449.5 U/L (sensitivity: 1; specificity: 0.43) and 551 pg/mL (sensitivity: 0.49; specificity: 0.86), respectively.

Conclusion：LDH and NTProBNP appear to be promising predictors of COVID-19 poor prognosis in the ICU. Larger sample size studies are required to confirm the validity of this combination of biomarkers.

Keywords: COVID-19, ICU, biochemical parameters, prognostic, biomarkers

1. Introduction

The Coronavirus disease 2019 (COVID-19) pandemic had caused over 195 million infections and over 4.1 million deaths globally (JHU, 2021) as of 28th July 2021. South Africa (SA) was the worst affected country in Africa with up to 2.3 million confirmed cases and 70 338 deaths (JHU, 2021). A range of COVID-19 manifestations have been observed, ranging from asymptomatic, mild, moderate, severe, to fulminant (Wu et al., 2020). The severity of clinical presentations has been associated with high viral load, increasing age, and the presence of comorbidities (Jin et al., 2020), resulting in higher risks of acute respiratory distress syndrome (ARDS), acute renal, hepatic, or cardiac injury, and death (Huang et al., 2020). Several reports from Asia, Europe, and the USA indicate that deranged biochemical, inflammatory, and immunological parameters may be associated with a poor prognosis (Mehta et al., 2020; Thompson et al., 2020; Ferrari et al., 2020; Gao et al., 2020; Henry et al., 2020; Song et al., 2020; Karakoyun et al., 2021). Data on biochemical markers and the association with mortality observed in patients with severe COVID-19 disease admitted to Intensive Care Units (ICUs) in sub-Saharan Africa are scanty.

The aim of this study was to evaluate baseline routine biochemical findings in patients admitted to the ICU in a tertiary hospital in the Western Cape of South Africa during the second wave and correlate these to the severity of the disease.

1. Methods

1.1. Study population

This cohort study took place at Tygerberg Hospital, a 1380-bed tertiary hospital in Cape Town, South Africa. The hospital provides tertiary services to approximately 3.5 million people from the Western Cape Province.

The study population comprised 82 consecutive patients with a positive SARS-COV-2 polymerase chain reaction (PCR) test admitted to the adult ICU during the second wave between 29 October 2020 and 10 February 2021. These biochemical parameters were routinely collected in the ICU. Patients were triaged by the intensivists according to disease severity and likely prognosis, according to provincial guidelines (CCSSA, 2020), and admission was dictated by bed availability.

1.2. Data collection

Due to infection control risk, data were captured prospectively using photographs of written clinical notes at the bedside, which were securely stored electronically, and clinical data were entered remotely by data-capturer into a Redcap® database. Laboratory results were imported from the National Health Laboratory Service (NHLS) Laboratory Information System (TrakCare® Lab Enterprise) into the database. Data were quality checked by the 'data entry supervisor' to ensure that data entered were of good quality and reliable.

1.3. Ethics

Patient confidentiality was ensured by labelling data with a unique episode number. The study was approved by the Health Research Ethics Committee of Stellenbosch

University (approval number N20/04/002_COVID-19). The research project was conducted according to the ethical principles of the Declaration of Helsinki.

1.4. Laboratory analyses

Serum samples were collected on ICU admission on all study participants and analysed in the NHLS Chemical Pathology Laboratory on the Roche cobas® 6000 analyser (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's recommendations. The NHLS is the South African national state laboratory providing laboratory services to over 80% of the population. The levels of various parameters were determined as follows: sodium (Na^+) and potassium (K^+) using indirect ion-selective electrode potentiometry, creatinine enzymatically, urea using a kinetic assay with urease, alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) enzymatically, bilirubin using the colorimetric diazo method, C-reactive protein (CRP) immunoturbidimetrically and high-sensitivity troponin T (hs-TnT), N-terminal pro-brain natriuretic peptide (NT-proBNP), procalcitonin (PCT) and ferritin using an electrochemiluminescent immunoassay and glycated haemoglobin (HbA1c) using a turbidimetric inhibition immunoassay. The estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula without correction for the race; a calculation recommended by the Kidney Disease Improving Global Outcomes (KDIGO) report (Levey et al., 2020). The NHLS Chemical Pathology laboratory is accredited by the South African National Accreditation Services (SANAS), a regulatory body responsible for laboratory conformity to ISO15189 assessments in South Africa. Result quality is validated with internal quality control and the laboratory participates in an external quality control scheme.

1.5. Outcomes and predictors variables

Data collected included sociodemographic (age, sex), pre-existing comorbidities associated with severe COVID-19 outcome (hypertension, diabetes mellitus, and hyperlipidaemia), and routinely collected biochemistry. The primary outcome was the proportion of patients who died (non-survivors) after admission to the ICU. Time to death or discharge and length of stay in ICU was assessed.

1.6. Statistical analysis

Continuous variables were expressed as mean with standard deviation for normal data and median with inter-quartile range for non-normal data. Categorical variables were expressed using frequencies and percentages. Robust Poisson regression was used to assess the significant association between demographic, laboratory results, and survival. Factors associated with death at p-value < 0.15 in unadjusted univariable robust Poisson regression were included in a multivariable model to identify independent factors associated with death. Due to the high prevalence of mortality, around 66%, the logistic regression overestimated the effect measure with large standard errors resulting in wide confidence intervals, therefore robust Poisson regression was used. Adjusted incidence rate ratios and their 95% CIs were used as a measure of association. Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of various biochemical analytes to discriminate between severely diseased cases in terms of survival and non-survival. Factors with $p<0.05$ were considered significantly associated with mortality. All statistical analyses were performed using Stata (V.16, Stata Corp, College Station, Texas, USA) and R (V, 4.0.2, R Core Team) with R Studio (V.1.3, R Studio Team) statistical software.

2. Results

2.1. Patient demographics

In this cohort, 82 patients with a median age of 53.8 years (IQR: 46.4-59.7) were admitted from October 2020 to February 2021. Table 1 shows the demographic characteristics. There were 27 males (33%) and underlying comorbidities considered in this analysis were hypertension (n = 39, 57%), diabetes mellitus (n= 34, 50%) and hyperlipidaemia (n= 5, 7%).

The median duration of stay in ICU was 10 days (IQR: 5-14) days, and of the 82 in whom outcome data were available at database censure, 54/82 (66%) died in ICU. Table 1 is a descriptive table showing that there was no statistical difference between survivors and non-survivors admitted to ICU for demographic characteristics, age, sex, and comorbidities.

2.2. Baseline biochemical parameters

The association between baseline biochemical parameters in survivors and non-survivors is shown in table 2. Electrolyte results, namely Na^+ and K^+ showed no significant differences between the 2 groups (p= 0.37 and 0.51 respectively). Markers of renal function showed no significant difference in urea and creatinine levels between the 2 groups (p=0.18 and 0.097 respectively), however, the eGFR was decreased (p=0.046) in the non-survivor group. HbA1c showed no statistical difference between survivors and non-survivors (p=0.33).

Markers of liver function showed no significant difference in bilirubin and ALT between the 2 groups (p= 0.65 and 0.81 respectively), but the non-specific marker LDH was significantly increased in non-survivors (p=0.014). Markers of cardiac function showed significantly increased levels of TnT and NT-proBNP in non-survivors (p=0.006 and 0.004 respectively). Markers of inflammation showed significantly higher levels of CRP and PCT in non-survivors (p= 0.014 and 0.003 respectively). Even though ferritin levels were increased, there was no statistically significant difference between survivors and non-survivors (p= 0.88).

2.3. Association of socio-demographic and biochemical parameters with survival

Table 3 shows the association between socio-demographic and biochemical parameters with survival in our cohort. In unadjusted univariate analysis, the risks ratio was statistically significant for urea (1.03, 95%CI: 1.01-1.06; p = 0.020), creatinine (1.01, 95%CI: 1.01-1.07, p = 0.003), eGFR (0.99, 95%CI: 0.98-0.99; p = 0.005), LDH (1.01, 95%CI: 1.01-1.04; p = 0.001), TnT (1.02, 9%CI: 1.01-1.03; p = 0.012), NTProBNP (1.01, 95%CI: 1.01-1.03; p = 0.001), CRP (1.02, 95%CI: 1.03-1.04, P = 0.021) and PCT (1.21, 95%CI: 1.10-1.35; p<0.001). However, LDH and NT-ProBNP also showed a significant association with poor prognosis in adjusted univariate analysis with respectively (aRR: 1.002, 95%CI: 1.0004-1.004; p = 0.016) and (aRR: 1.0004, 95%CI: 1.0001-1.0007; p = 0.014).

2.4. Cut-offs and ROC

As the adjusted RR was significant for LDH and NTProBNP, we determined the optimal cut-offs to predict non-survival and test the performance of these two parameters using ROC curves. The proposed optimum cut-off points for LDH and NT-ProBNP that could predict COVID-19 severity and mortality in the ICU were respectively ≥ 449.5 U/L with sensitivity = 100%, specificity = 43%, AUC = 0.73 and ≥ 551 pg/mL with sensitivity = 49%, specificity = 86%, AUC = 0.72 (Table 4). However, the performance of both was suboptimal to use as a prediction marker on their own (see figure 1).

3. Discussion

Although numerous studies globally have evaluated biochemical abnormalities in the first and second waves of COVID-19 (Mehta et al., 2020; Thompson et al., 2020; Ferrari et al., 2020; Gao et al., 2020; Henry et al., 2020; Song et al., 2020; Karakoyun et al., 2021), there is a paucity of data from Africa. South Africa experienced the second wave in late 2020 and this study examined patients admitted to the ICU during that period.

There were several notable findings from this study, including the observation that in non-survivors the eGFR was significantly decreased while the LDH levels were significantly increased. Furthermore, surrogate markers of cardiac dysfunction, namely TnT and NT-proBNP, and inflammatory markers, namely CRP and PCT, were significantly elevated among non-survivors. However, only LDH and NT-proBNP were significant predictors of disease severity.

Other biochemical parameters such as serum Na^+ and K^+ (Chen et al., 2020; Lippi et al., 2020; Wang et al., 2020), CRP (Bonetti et al., 2020; Luo et al., 2020; Ponti et al., 2020; Tan et al., 2020; Yamada et al., 2020; Poggiali et al., 2020; Boufrioua et al., 2021), PCT (Ponti et al., 2020; Lippi and Plebani, 2020; Hesse et al., 2021), pro-inflammatory cytokines, albumin, and ferritin are biomarkers that have been linked with multi-organ failure among severe COVID-19 patients admitted in the ICU (Mehta et al., 2020; Thompson et al., 2020; Zeng et al., 2020) were not significantly associated with COVID-19 after adjustment for confounders. However, several markers of organ dysfunction have been described as prognostic markers in COVID-19. These include hepatocyte injury (bilirubin, ALT, and the nonspecific enzyme, LDH) (Bonetti et al., 2020; Poggiali et al., 2020; Kermali et al., 2020), renal function test (urea, creatinine, and eGFR) (Henry et al., 2020a; Henry and Lippi, 2020) and cardiac function tests (hs-TnT and NT-proBNP) (Lippi et al., 2020a; Gao et al., 2020a). Biochemical markers associated with severity include raised LDH, CRP, cardiac troponins, and NT-proBNP.

To our knowledge, there is only one study on biomarkers in the first wave. A study by Hesse et al investigated laboratory findings of all patients with Covid-19 during a 4-month period (11.7% positive) and found that disease severity was associated with raised inflammatory markers, coagulation markers, liver and cardiac markers, and urea (Hesse et al., 2021). Two studies compared the first and second waves in South Africa. Jassat et al only compared clinical outcomes and described more hospitalizations in patients who were older with fewer comorbidities and a 20% increased risk of in-hospital mortality (Jassat et al., 2021). Maslo et al compared clinical and laboratory data in patients hospitalised in one hospital during both waves and found that patients admitted during the second wave were also older with fewer comorbidities and had significantly higher D-dimer and interleukin (IL)-6 levels (Maslo et al., 2021). As these findings are thought to be due to increased transmissibility of the variants of concern, other laboratory biomarkers may be useful to predict disease severity.

In our cohort, we examined routine biochemical tests which included electrolytes, markers of renal, hepatic, and cardiac dysfunction as well as markers of inflammation and correlated them with survival.

As hepatocytes express angiotensin-converting enzyme (ACE)-2 receptors, liver damage may be due to direct infection (Chai et al., 2020), but also due to hepatotoxic drugs, systemic inflammatory response, hypoxia, or multiorgan failure (Feng et al., 2020). In our cohort, we found no significant difference in bilirubin or ALT levels, however, LDH was significantly raised in non-survivors. This agrees with previous studies and high LDH was one of the first markers of disease severity described (Poggiali et al., 2020; Kermali et al., 2020; Ciacco et al., 2020; Ferrari et al., 2020). LDH is not liver-specific and this increase in LDH is thought to be due to lung damage induced by SARS-CoV-2 (Han et al., 2020). It must be noted that even though levels were significantly higher in the non-survivors in our cohort, both groups had levels well above the higher reference limits, like the observation by Kermali et al (Kermali et al., 2020).

The risk of cardiac dysfunction is increased in COVD-19 and possible causes include direct cytopathic injury due to the presence of ACE2 receptors on cardiac myocytes, cytokine-mediated damage, ischaemia, or exacerbation of pre-existing cardiac disease (Akhmerov and Marbán, 2020; Khan et al., 2020). Like previous studies, we found significantly higher TnT and NT-proBNP levels in non-survivors (Lippi et al., 2020; Gao et al., 2020). The American College of Cardiology (ACC) stated that increased TnT and NT-proBNP levels do not necessarily suggest acute coronary syndrome and must be interpreted in the correct clinical context taking the clinical picture of the patient into consideration (ACC, 2020).

The cytokine storm in COVID-19 is associated with worse outcomes and increased levels of pro-inflammatory cytokines such as IL-6 (Mehta et al., 2020; Song et al., 2020). This affects acute phase reactants leading to increased CRP and ferritin and decreased albumin levels (Mehta et al., 2020). Most laboratories, including ours, do not routinely analyse IL-6. However, CRP is synthesized in the liver under the influence of IL-6 and therefore reflects IL-6 levels (Boras et al., 2014; Sproston and Ashworth, 2018). We found significantly increased CRP levels in non-survivors which agrees with published literature (Bonetti et al., 2020; Luo et al., 2020; Ponti et al., 2020; Tan et al., 2020; Yamada et al., 2020; Poggiali et al., 2020; Boufrioua et al., 2021). Unfortunately, albumin was not measured routinely in our patients and therefore numbers were too few to analyse.

PCT is normally produced in the C-cells of the thyroid and levels are undetectable in health. However, during infection (especially bacterial) levels rise due to extra-thyroidal synthesis (Karzai et al., 2020). We found increased PCT levels in non-survivors which is also consistent with other studies (Ponti et al., 2020; Lippi and Plebani, 2020; Hesse et al., 2021). Although previous studies have found increased ferritin (Cheng et al., 2020) or no difference (Wu et al., 2020) between COVID-19 survivors and non-survivors, we found increased levels in survivors. However, this difference was not statistically significant, and our numbers were small.

When analysing the unadjusted risk ratio in our cohort, urea, creatinine, eGFR, LDH, TnT, NT-proBNP, CRP, and PCT were significantly associated with the risk of non-survival. However, using adjusted RR, only LDH and NT-proBNP were significantly associated with risk. We then determined optimal cut-offs of these 2 analytes to predict severity. However, the performance of both was suboptimal to use on their own as predictive markers.

Chronic kidney disease is associated with worse outcomes in COVID-19 (Henry and Lippi, 2020). In our study, we found slightly higher urea and creatinine with lower eGFR levels in non-survivors, but these differences were neither statistically nor clinically significant. Other studies have described higher urea levels to be associated with severity (Bonetti et al., 2020; Boufrioua et al., 2021).

We found no significant differences in Na^+ and K^+ levels between survivors and non-survivors. Few studies have evaluated electrolyte disturbances in COVID-19 (Chen et al., 2020; Lippi et al., 2020; Wang et al., 2020) and many have reported hypokalaemia to be associated with worse outcomes and exacerbation of ARDS and cardiac injury. As the SARS-CoV-2 virus enters the cells using the ACE2 receptor and thereby influences the renin-angiotensin system renal loss of K^+ is thought to be the cause of electrolyte disorders in these patients (Chen et al., 2020; Lippi et al., 2020). Electrolytes may be also influenced by other clinical manifestations of these patients such as gastro-intestinal loss due to diarrhoea and vomiting and multiorgan failure (Chen et al., 2020).

Our findings also showed that non-survivors were slightly older, more likely to be male and smokers, there was no statistical difference between the two groups. Comorbidities such as hypertension and diabetes mellitus have been shown to be predictors of non-survival (Savoia et al., 2021; Prattichizzo et al., 2021). The association of hypertension with the severe outcome has been postulated to be because of the SARS-CoV-2 on the RAS (Savoia et al., 2021). Diabetes mellitus with high HbA1c is associated with worse SARS-CoV-2 outcomes (Prattichizzo et al., 2021). However, in our cohort, although 57% of the participants were hypertensive, we found no significant difference between survivors and non-survivors for hypertension or diabetes mellitus.

It must however be noted that the median HbA1c levels were raised at > 7% in both groups. A level of > 6.5% is diagnostic of diabetes. Our results agree with a recent study conducted in South Africa (Hesse et al., 2021).

Our study had some limitations. We had a small population and only analysed baseline ICU admission laboratory data. A larger sample population may have increased the statistical significance of our markers. Ideally, we would have analysed the trend over their ICU stay, but the numbers were too small on subsequent days. Our study had certain strengths, namely, all patients were admitted to the same ICU and had samples analysed on admission in the same laboratory ensuring harmonization of the pre-analytical and analytical phases of testing. Further larger studies are needed to evaluate these biomarkers to determine their use in developing a risk score as earlier identification of patients at high risk of poor prognosis and institution of early interventions may be effective in reducing COVID-19 mortality among patients admitted in the ICU.

4. Conclusion

Our study identified LDH and NT-proBNP biochemical markers which may be associated with poor COVID-19 outcomes in patients admitted to the ICU. To increase predictive probability there is a need to combine biomarkers assessment and not only rely on a single parameter estimate. i.e., combining LDH and NT-proBNP increases the sensitivity of predicting mortality rather than relying on a single biomarker.

5. Abbreviations

ACC: American College of Cardiology; ACE: angiotensin-converting enzyme; ALT: alanine aminotransferase; aRR: adjusted Relative Risk; ARDS: Acute Respiratory Distress Syndrome; AST: aspartate aminotransferase; AUC: Area Under the Curve; CCSSA: Critical Care Society of Southern Africa; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CRP: C-reactive protein; COVID-19: Coronavirus Disease 2019; eGFR: estimated glomerular filtration rate; HbA1c: Haemoglobin A1C; hs-TnT: high-sensitivity troponin T; ICU: intensive unit care; IL: interleukin; KDIGO: Kidney Disease Improving Global Outcomes; IQR: interquartile range; K+: Potassium; LDH: Lactate Dehydrogenase; Na+ : Sodium; NHLS: National Health Laboratory Service; NTProBNP: N-terminal pro b-type natriuretic peptide; PCR: Polymerase Chain Reaction; PCT: procalcitonin; RAS: renin-angiotensin system; ROC: Receiver Operating Characteristic; SA: South Africa; SANAS: South African National Accreditation Services; SARS-COV-2: Severe acute respiratory syndrome coronavirus 2; TnT: Troponin T

6. Footnotes

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Informed Consent Statement: The Investigators obtained ethical approval and waiver of consent from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University, and the Research Committee of the Tygerberg Hospital Ethics approval number N20/04/002_COVID-19.

Conflicts of Interest: No conflict of interest declared

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LEGENDS TO FIGURES AND TABLES

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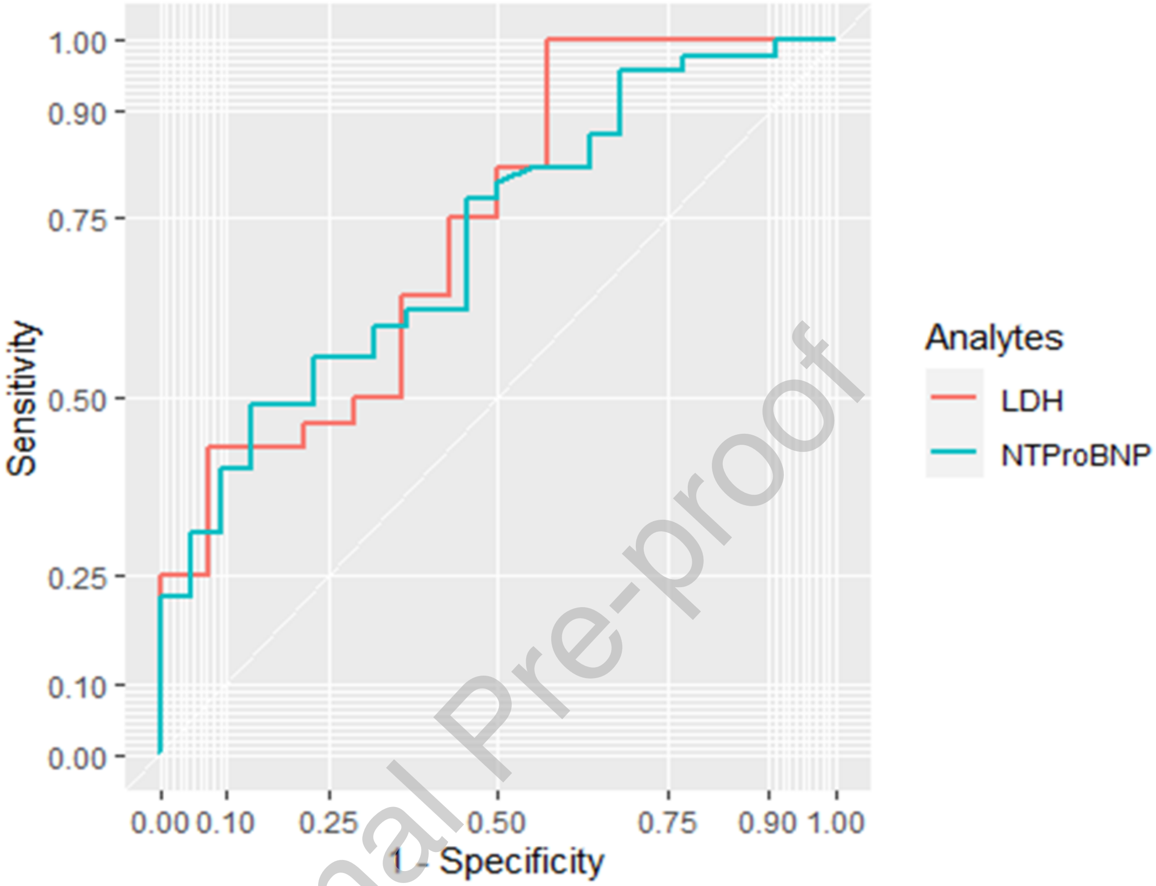

Figure 1: ROC curve of predictor effect of combined LDH (Lactate Dehydrogenase) and NT-proBNP (N-terminal pro B-type natriuretic peptide) for poor prognosis

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Table 1: Demographic characteristics of COVID-19 patients admitted in the ICU

Characteristic	Total (%)	Survivors (N = 28)	Non-survivors (N = 54)	p-value
Age (in years) Median (IQR)	53.8 (46.4-59.7)	49.6 (42.0-60.2)	55.3 (47.2-58.1)	0.31
Gender (Male)	27 (33%)	8 (29%)	19 (35%)	0.55
Smoker	13 (25%)	3 (17%)	10 (27%)	0.67
Duration of ICU stay	10 (5-14)	9.5 (5.5-14)	10 (5-13)	0.88
Hypertension	39 (57%)	12 (55%)	27 (59%)	0.75
Diabetes mellitus	34 (50%)	12 (55%)	22 (48%)	0.6
Hyperlipidaemia	5 (7%)	1 (5%)	4 (9%)	0.54

Table 2: Baseline biochemical characteristics of COVID-19 patients admitted to the ICU

Analytes	Total	Reference Intervals	Median (IQR)	Discharge N=28	Death N=54	P
Na^+	82	135-145 mmol/L	137.5 (135-140)	137 (135-139.5)	138 (135-141)	0.37
K^+	82	3.5-5.1 mmol/L	4.4 (3.8-4.7)	4.2 (3.8-4.7)	4.4 (3.9-4.7)	0.51
Urea	82	2.1-7.1 mmol/L	6.3 (4.9-8.3)	5.95 (4.4-7.9)	6.5 (5.1-8.8)	0.18
Creatinine	82	49-90 µmol/L	73.5 (64-98)	71 (63-78)	75.5 (66-107)	0.097
eGFR	82	>60 ml/min	83 (71-99)	88 (75.5-104.5)	80 (70-94)	0.046
HbA1c	77	<6.5%	7.6 (6.3-8.7)	7.8 (6.3-11.6)	7.5 (6.3-8.4)	0.33
Ca^{2+}	58	2.12-2.59 mmol/L	2.07 (2.02-2.17)	2.1 (2.03-2.19)	2.06 (2.01-2.16)	0.45
Mg^{2+}	53	0.63-1.05 mmol/L	0.94 (0.88-1.07)	0.89 (0.81-0.94)	0.98 (0.89-1.08)	0.019
Phos	53	0.78-1.42 mmol/L	1.15 (0.94-1.53)	1.16 (1.09-1.35)	1.14 (0.93-1.55)	0.94
Tbili	73	5-21 µmol/L	7 (5-9)	7 (5-9)	7 (5-9)	0.65
ALT	74	<41 U/L	38.5 (23-50)	40 (23-65)	37 (22-49)	0.81
LDH	42	100-190 U/L	722 (579-900)	606 (346-846)	772 (633-957.5)	0.014
TnT	68	<100 ng/L	13.5 (6-28)	6 (5-16)	15 (9-37)	0.006
NTProBNP	67	<125 pg/mL	220 (102-845)	116 (63-259)	309 (125-1390)	0.004
CRP	81	<10 mg/L	147 (96-221)	106.5 (69.5-186.5)	162 (110-235)	0.014
PCT	70	<0.5 ng/mL	0.36 (0.13-1.12)	0.16 (0.08-0.36)	0.57 (0.19-1.68)	0.003
Ferritin	61	13-150 ug/L	891 (440-1400)	937 (344-1400)	770 (440-1496)	0.88

Note: Na^+: Sodium, K^+: Potasium, eGFR: estimated glomerular filtration rate, HbA1c: Hemoglobin A1C, Ca^{2+}: calcium, Mg^{2+}: Magnesium, Phos: Phosphate, Tbili: Total bilirubin, ALT: alanine aminotransferase, LDH: Lactate Dehydrogenase, TnT: Troponin T, NT-ProBNP: N-terminal pro b-type natriuretic peptide, CRP: C-reactive protein, PCT: procalcitonin

Table 3: Association of socio-demographic and biochemical parameters with mortality status among patients admitted to the COVID-19 ICU

Characteristic	Unadjusted RR (95% CI)	p-value	Adjusted RR (95% CI)	p-value
Age	1.00 (0.99-1.03)	0.308	-	-
Gender: Male	1.19 (0.86-1.64)	0.298		
Duration in ICU stay	0.99 (0.97-1.01)	0.424		
Hypertension	1.06 (0.75-1.48)	0.75		
Asthma	0.73 (0.18-2.99)	0.665		
Diabetes Mellitus	0.92 (0.66-1.28)	0.608		
Hyperlipidaemia	1.20 (0.75-1.93)	0.452		
Na^+	1.01 (0.97-1.04)	0.722		
K^+	1.10 (0.90-1.35)	0.370		
Urea	1.03 (1.01-1.06)	0.020	0.86 (0.74-1.01)	0.073
Creatinine	1.01 (1.01-1.07)	0.003	0.99 (0.98-1.01)	0.530
eGFR	0.99 (0.98-0.99)	0.005	0.99 (0.97-1.01)	0.453
HbA1c	0.95 (0.87-1.03)	0.206		
Ca^{2+}	0.95 (0.27-3.39)	0.941		
Mg^{2+}	1.02 (0.44-2.39)	0.956		
Phos	1.13 (0.95-1.35)	0.172		
Tbili	1.01 (1.00-1.03)	0.667		
ALT	1.00 (0.99-1.00)	0.631		
LDH	1.01 (1.01-1.04)	0.001	1.002 (1.0004-1.004)	0.016
TnT	1.02 (1.01-1.03)	0.012	0.99 (0.98-1.004)	0.199
NTProBNP	1.01 (1.01-1.03)	0.001	1.0004 (1.0001-1.0007)	0.014
CRP	1.02 (1.03-1.04)	0.021	1.001 (0.999-1.003)	0.251
PCT	1.21 (1.10-1.35)	<0.001	1.14 (0.96-1.36)	0.135
Ferritin	1.00 (0.99-1.00)	0.893		

Note: Na^+: Sodium, K^+: Potasium, eGFR: estimated glomerular filtration rate, HbA1c: Hemoglobin A1C, Ca^{2+}: calcium, Mg^{2+}: Magnesium, Phos: Phosphate, Tbili: Total bilirubin, ALT: alanine aminotransferase, LDH: Lactate Dehydrogenase, TnT: Troponin T, NTProBNP: N-terminal pro b-type natriuretic peptide, CRP: C-reactive protein, PCT: procalcitonin

Table 4: Optimal cutoff, sensitivity, specificity, and AUC for LDH (Lactate Dehydrogenase) and NT-proBNP (N-terminal pro B-type natriuretic peptide)

Analyte	Direction	Optimal cutpoint	Sensitivity	Specificity	AUC
LDH	>=	449.5	1	0.43	0.73
NT-proBNP	>=	551	0.49	0.86	0.72